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APPLICATION NUMBER: 60/201,730

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## BERESKIN &amp; PARR

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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

INVENTOR(S)					
Given Name (first and middle (if any))		Family Name or Surname		Residence (City and either State or Foreign Country)	
Andrei K. L. James P.		Yudin Martyn		Toronto, Canada Mississauga, Canada	
<input type="checkbox"/> Additional inventors are being named on the _____ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (280 characters max) Nucleophilic Modification of Polyfluorinated Catalysts					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
<input checked="" type="checkbox"/> Customer Number		1059		Place Customer Number Bar Code Label here	
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ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification Number of Pages		9		<input type="checkbox"/> Small Entity Statement	
<input checked="" type="checkbox"/> Drawing(s) Number of Sheets		10		<input type="checkbox"/> Other (specify) _____	
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)					
<input type="checkbox"/> A check or money order is enclosed to cover the filing fees		FILING FEE AMOUNT (\$)			
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number		02-2095		\$150.00	
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government. <input checked="" type="checkbox"/> No. <input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are: _____					

Respectfully submitted,

SIGNATURE

Michelle Gravelle

Date May 4/00

TYPED or PRINTED NAME

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REGISTRATION NO.  
(if appropriate)  
Docket Number:

40,261

11699-2

**USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT**

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C., 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C., 20231.

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05/04/00

BERESKIN & PARR

UNITED STATES

60201730-050400

Title: NUCLEOPHILIC MODIFICATION OF POLYFLUORINATED  
CATALYSTS

Inventor: ANDREI K. YUDIN and L. JAMES P. MARTYN

B&P File No. 11699-2/MG

**Title: NUCLEOPHILIC MODIFICATION OF POLYFLUORINATED CATALYSTS**

**FIELD OF THE INVENTION**

5           The present invention relates to the nucleophilic modification of polyfluorinated catalysts.

**BACKGROUND OF THE INVENTION**

10           Modern asymmetric synthesis demands new and improved catalytic transformations. Understanding the balance of steric and electronic factors is required in order to fine-tune a catalyst to achieve optimal rate and selectivity in a particular reaction. A lot of research in recent years has been devoted to the development of chiral ligands. Among these, 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) and related molecules with axial chirality (such as BINAP, MOP, BIMOP) have found  
15           wide utility in asymmetric catalysis. Over the years, several modifications of the BINOL skeleton aimed at changing its steric as well as electronic properties have been reported. Thus, partially hydrogenated BINOL was used in enantioselective alkylation of aldehydes, conjugate addition of diethylzinc to cyclic enones, and ring-opening of epoxides. Incorporation  
20           of bromine atoms at the 6 and 6' positions of BINOL, rather remote from the catalytic site, was shown to increase the enantioselectivity of the corresponding titanium catalysts in glyoxylate-ene reactions. Bulky triarylsilyl groups at the 3 and 3' positions of BINOL led to increased levels of enantiofacial discrimination of prochiral aldehydes in asymmetric  
25           Diels-Alder reactions. 3,3'-Dinitrooctahydrobinaphthol was applied in titanium-catalyzed asymmetric oxidation of methyl-*p*-tolylsulfide.

          The inventors have demonstrated that substitution of hydrogens by fluorines at the 5, 5', 6, 6', 7, 7', 8 and 8' positions of BINOL induces considerable electronic and minimal steric perturbations of the  
30           aromatic system in the resulting 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl (F<sub>8</sub>BINOL). (U.S. Provisional application no. 60/144,812 which is incorporated herein by reference in its entirety). Comparison of

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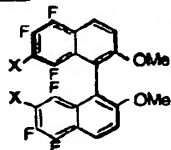
electrostatic potential surfaces (AM1) of BINOL and F<sub>8</sub>BINOL revealed a noticeable difference in the distribution of electron density. The electron-deficient nature of the aromatic rings raised the oxidative stability of F<sub>8</sub>BINOL compared to BINOL as well as increases the acidity of the ring-bound hydroxyl groups. The inventors originally proposed that this could translate into high stability and modulated binding to metals as well as reactants in F<sub>8</sub>BINOL-mediated processes. The inventors subsequently discovered a dramatic increase in configurational stability of homochiral F<sub>8</sub>BINOL compared to BINOL with electronic effects playing a decisive role. Catalytic asymmetric sulfoxidation experiments with Ti(IV)/F<sub>8</sub>BINOL catalyst indicate that fluorine substitution leads to improved levels of enantioselectivity and dictates a reversal in the sense of chiral induction.

Impressive enantioselectivities were achieved in the hetero Diels-Alder reactions between the Danishefsky diene and aldehydes. Most importantly, the concept of electronic perturbation of the BINOL scaffold is working despite initial concern that octafluorination could drastically decrease binding to transition metals.

#### SUMMARY OF THE INVENTION

The present invention relates to improved polyfluorinated catalysts through the nucleophilic modification of polyfluorinated catalysts. The modification consists of displacing fluorine atoms of a polyfluorinated catalyst with a nucleophile. In particular, the present inventors have selectively displaced the fluorine atoms at positions 7 and 7' of 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl (F<sub>8</sub>BINOL) with a nucleophile.

Accordingly, the present invention provides a modified polyfluorinated catalyst having the formula:



wherein X can be any nucleophile including OR, NR<sub>2</sub>, SR and wherein R can be any group including an aliphatic group; an aromatic group, a vinylic group, an acetylenic group or a heteroatom.

Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described in relation to the drawings in which:

Figure 1 shows the preparation of a modified polyfluorinated catalyst.

Figure 2 shows the configurational integrity of the polyfluorobinaphthyl core during nucleophilic modification.

Figure 3 is a schematic diagram showing the chemistry at the 7 and 7' positions of the modified catalyst.

Figure 4 shows the attachment of a modified catalyst to an electrode surface.

Figure 5 shows experimentally observed cyclic voltammogram for the modified electrode surface.

Figure 6 shows the attachment of a modified catalyst to a solid surface.

Figure 7 shows the nucleophilic substitution at the 5, 5' positions of the modified catalyst.

Figure 8 is a schematic showing the chemistry of the nucleophilic modification at the 5 and 5' positions.

Figure 9 illustrates internal nucleophilic displacement in monoprotected F<sub>8</sub>BINOL.

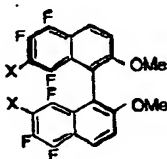
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Figure 10 illustrates a synthesis scheme for preparing  $H_4F_4$  ligands.

#### DETAILED DESCRIPTION OF THE INVENTION

As hereinbefore mentioned, the present invention relates to the nucleophilic modification of fluorinated catalysts. In particular, the present invention relates to the selective displacement of fluorine atoms with nucleophiles on a polyfluorinated catalyst such as the catalyst 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl ( $F_8$ BINOL).

In one embodiment, the present invention provides a modified  $F_8$ BINOL wherein the fluorine atoms at positions 7 and 7' have been selectively displaced with a nucleophile X and having the formula:



wherein X can be any nucleophile including OR,  $NR_2$ , SR and wherein R can be any group including an aliphatic group; an aromatic group, a vinylic group, an acetylenic group or a heteroatom.

In a specific embodiment, the nucleophile X is an OR group and the modified catalyst is prepared from the bis (methyl) ether of  $F_8$ BINOL according to the reaction scheme shown in Figure 1. Preferably, the nucleophile OR is a methoxy group (OMe). The inventors have shown that selective substitution of the fluorine groups at the 7 and 7' positions with the methoxy group takes place in 95% yield with remarkable selectivity. The configuration integrity of the polyfluorobinaphthyl core during the methoxylation process is shown in Figure 2.

Using the methoxylation process to develop the modified catalysts the inventors will now be able to develop combinatorial approaches to catalyst development. The inventors can determine which substitution pattern on the  $F_8$ BINOL moiety gives optimal catalyst with

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regard to rate and selectivity in a particular reaction. To address this issue, the dihedral angle and electron distribution in  $F_8$ BINOL will be varied by replacing fluorines at the 7,7' positions with a variety of XH nucleophiles to develop analogs of  $F_8$ BINOL.

5 The inventors will be able to generate libraries of such analogs using solution and solid-phase parallel synthesis. The structure/activity relationships will be deciphered based on screening the resulting catalyst libraries in a variety of reactions including hetero Diels-Alder, aziridination, direct aldol, and imine hydrogenation processes.

10 Figure 3 is a schematic diagram showing the chemistry of the modified catalyst at the 7 and 7' positions. The favourable conformation of the modified catalyst leads to many improved properties and utilities for the catalyst. For example, facile modification at the 7,7' positions suggests the possibility of placing the catalytic reaction center in that area.

15 Direct connection of heteroatoms by nucleophilic substitution should lead to novel  $C_2$  symmetrical ligands. Their monodentate nature will result from the steric constraints that should defeat chelation. In order to create different bidentate sites at the 7,7' position, linkers of varied lengths will be inserted into the X-C(7) and X-C(7') bonds.

20 The highly selective nucleophilic functionalization of the  $F_8$ BINOL core will allow the attachment of the modified catalysts to an electrode surface or a solid support. Figure 4 shows the attachment of the modified catalyst to an electrode surface and Figure 5 shows experimentally observed cyclic voltammogram for the modified electrode surface. Figure 6 shows the attachment of the modified catalyst to a solid support. In particular, Figure 6 exemplifies an approach toward libraries of TentaGel S OH resin-linked catalysts. An alternative to the strategy is to introduce functionality X directly onto the ligand-derivatized resin. On-bead screening for the catalytic activity will allow the fine-tuning of the ligand's torsion angle using solid-phase chemistry by manipulating the 7,7' substituents. It should be emphasized that established routes to modified BINOL involve rather harsh *electrophilic* functionalization

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which puts substituents into the 6,6' positions and necessitates a subsequent resolution step which is not feasible under combinatorial protocols commonly performed on a microgram scale. On the contrary, high configurational stability of  $F_8$ BINOL under basic conditions will

5 enable the use the homochiral starting material without the loss of enantiomeric purity during the nucleophilic substitution. As well, substituents at the 7,7' positions could have direct steric influence over the dihedral angle which should modulate the catalytic activity, a feature not available for the 6,6' substitution pattern.

10 In addition to the nucleophilic displacement of the fluorine atoms at positions 7 and 7', the present invention also includes the nucleophilic displacement of other fluorine atoms in the  $F_8$ BINOL catalyst. Figure 7 shows the selective displacement of the fluorine atoms at positions 5 and 5' with the nucleophiles X and Y in a modified  $F_8$ BINOL

15 containing A, B or C groups at positions 7 and 7'. Figure 8 shows the stereochemistry of a modified  $F_8$ BINOL containing nucleophiles at the 5, 5', 7 and 7' positions.

Figure 9 shows internal nucleophilic displacement in monoprotected  $F_8$ BINOL which illustrates that the axial chirality of

20  $F_8$ BINOL provides convenient access to ligands with helical chirality.

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and

25 equivalent arrangements included within the spirit and scope of the appended claims.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and

30 individually indicated to be incorporated by reference in its entirety.

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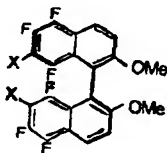
We Claim:

1. A modified 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl (F<sub>8</sub>BINOL) catalyst wherein the fluorine atoms at positions (a) 5 and 5' and/or (b) 6 and 6' and/or (c) 7 and 7' and/or (d) 8 and 8' have been selectively displaced with a nucleophile.

2. A modified catalyst according to claim 1 wherein the fluorine atoms at position 7 and 7' are selectively displaced with the nucleophile.

3. A modified catalyst according to claim 2 wherein the fluorine atoms at positions 5 and 5' are displaced with a nucleophile.

10 4. A modified polyfluorinated catalyst having the formula



wherein X can be any nucleophile including OR, NR<sub>2</sub>, SR and wherein R can be any group including an aliphatic group; an aromatic group, a vinylic group, an acetylenic group or a heteroatom.

5. A modified polyfluorinated catalyst according to claim 4  
15 wherein X = OR, wherein R can be any group including an aliphatic group; an aromatic group, a vinylic group, an acetylenic group or a heteroatom.

6. A modified polyfluorinated catalyst according to claim 5 wherein R is methyl.

7. A modified polyfluorinated catalyst according to any one of  
20 claims 1 to 6 wherein the catalyst is linked to a solid support.

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8. A modified polyfluorinated catalyst according to any one of claims 1 to 6 wherein the catalyst is linked to an electrode surface.

9. A modified polyfluorinated catalyst wherein at least one fluorine atom is displaced with a nucleophile.

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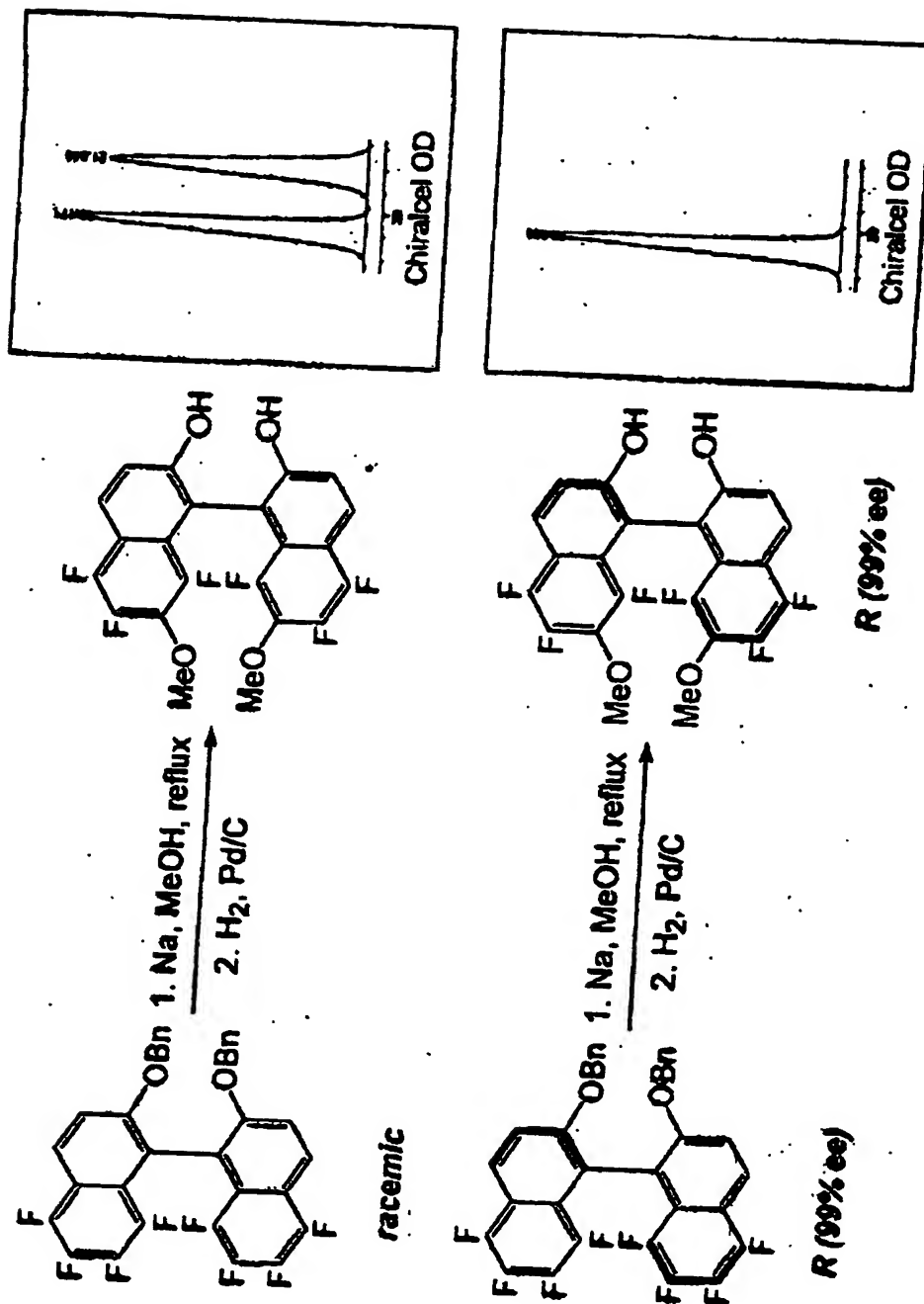
ABSTRACT OF THE DISCLOSURE

Modified 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-  
binaphthyl (F<sub>8</sub>BINOL) catalysts are described. The modification consists of  
5 selectively displacing the fluorine atoms of F<sub>8</sub>BINOL with a nucleophile.  
Modified catalysts in which the fluorine atoms at positions 7 and 7' of  
F<sub>8</sub>BINOL are of particular interest.

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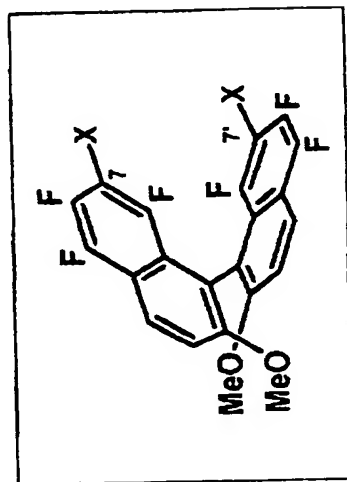


# **Configurational Integrity of the Polyfluorobinaphthyl Core During Nucleophilic Modification**



**FIGURE 3**

# Chemistry at the 7 and 7' Positions

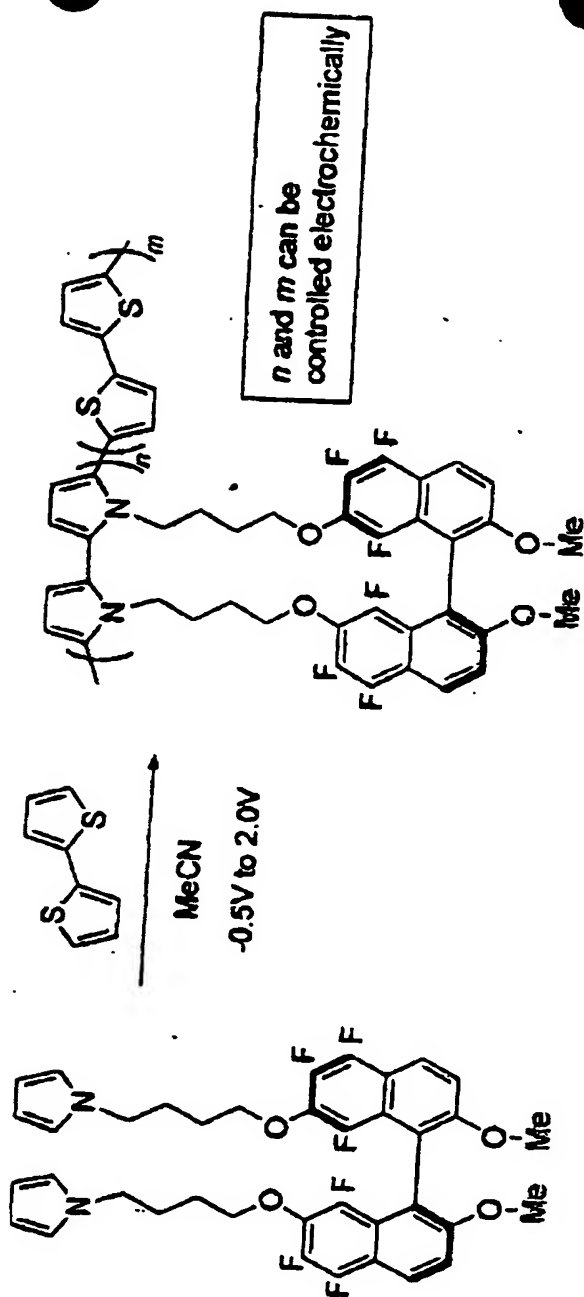


X

- steric control over the torsion angle
- further electronic alterations
- solid support
- new binding site
- catalyst libraries

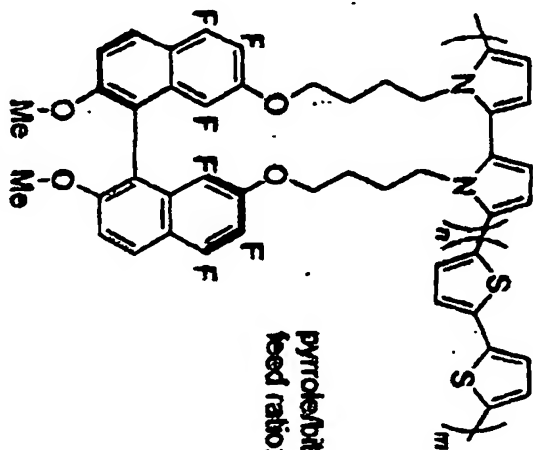
**FIGURE 4**

**F<sub>8</sub>BINOL Catalysts on Electrode Surfaces**





**FIGURE 5**



pyromellitimide  
feed ratio: 2:1

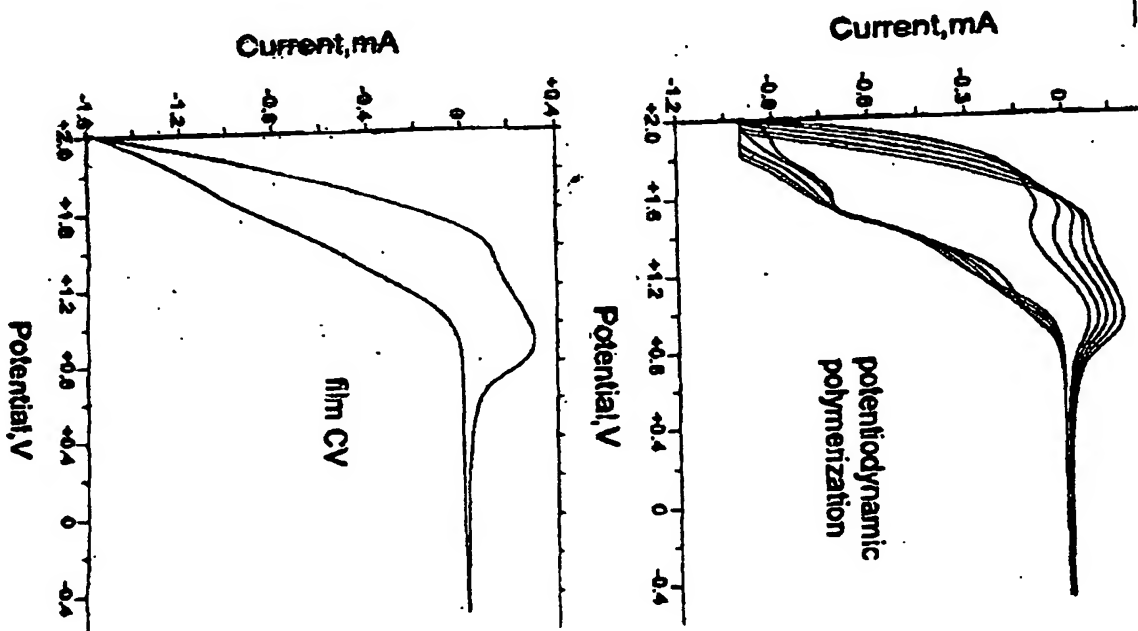
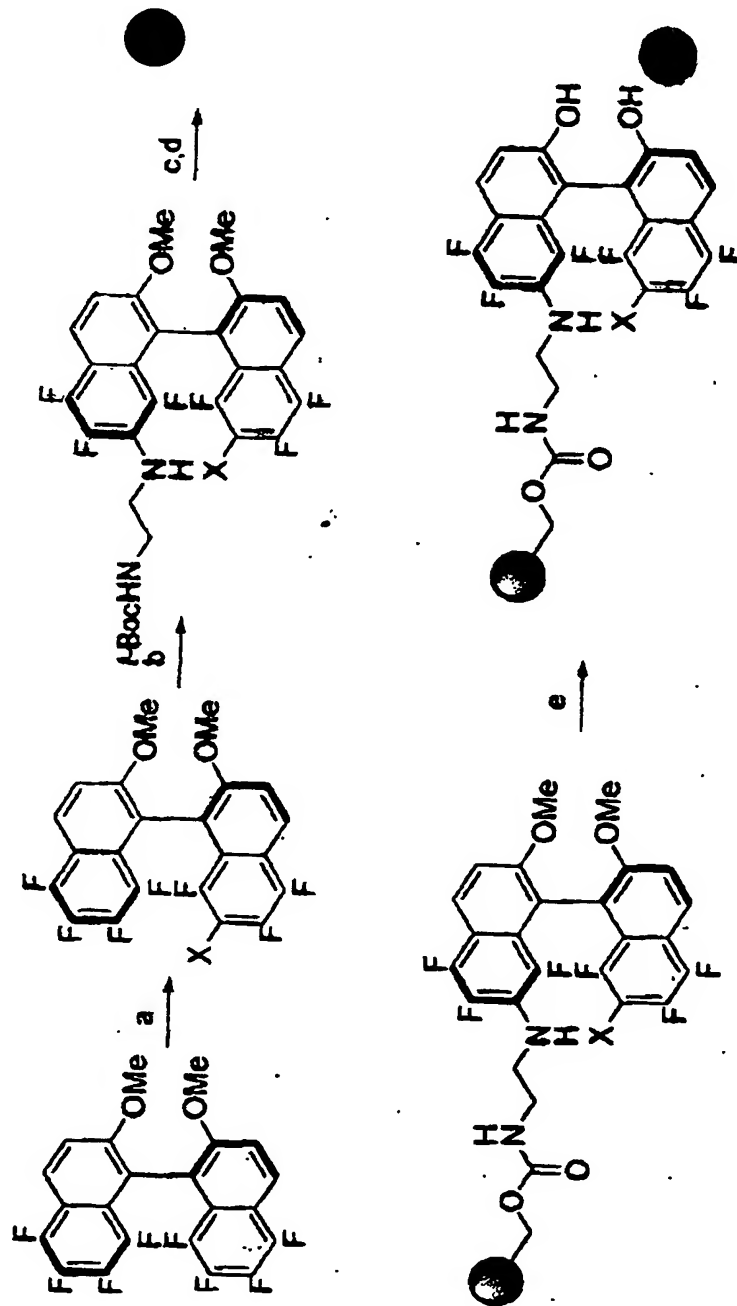
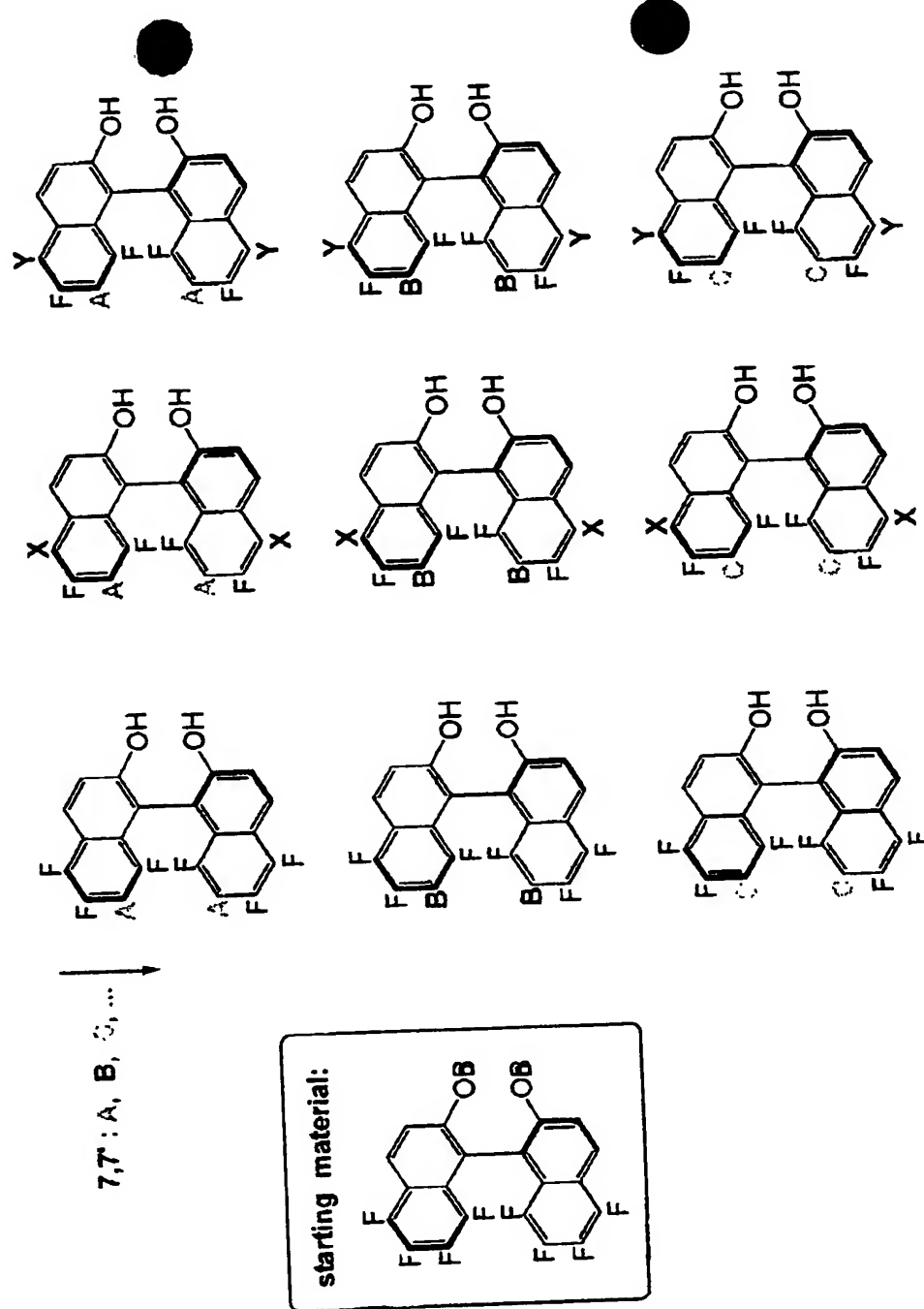


FIGURE 6

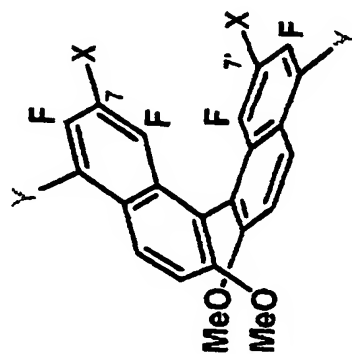
**F<sub>8</sub>BINOL Catalysts on the Solid Phase**

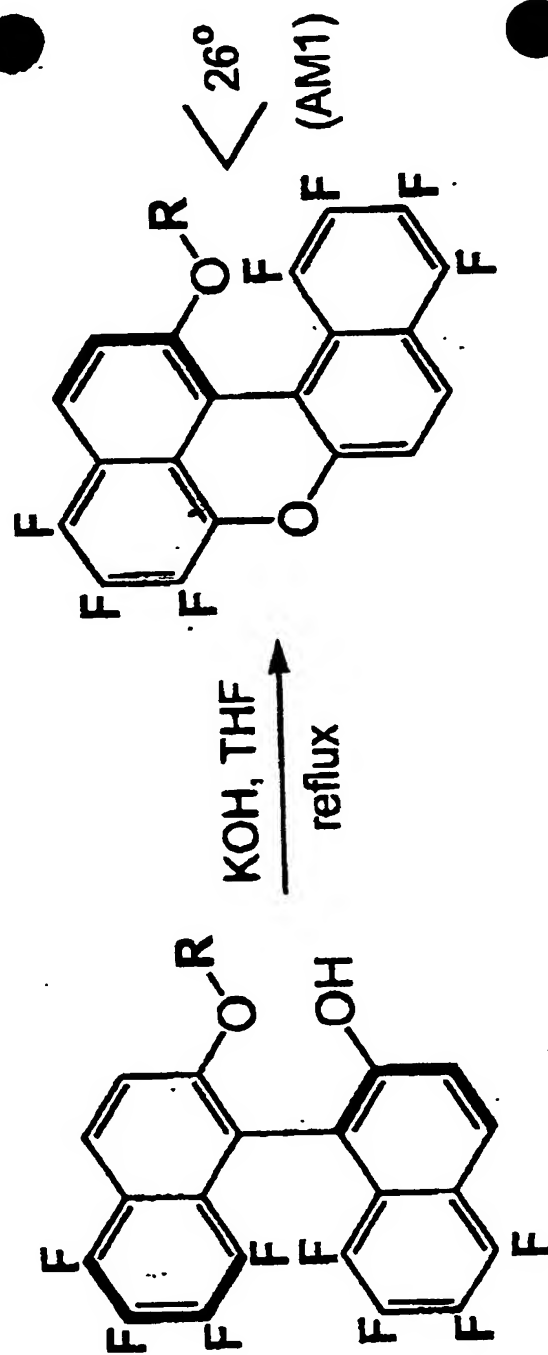
Key: a. XH (1 eq), toluene, 100 °C; b. NH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH(t-Boc); toluene, 100 °C; c. TFA, DCM; d. CDI, THF, TentaGel S OH; e. Pd-C, HCOONH<sub>4</sub>, MeOH, reflux

# **F<sub>n</sub>BINOL: Positional Scanning via Nucleophilic Substitution**



**FIGURE 8**  
**Further Nucleophilic Modification: 5 and 5'**  
**Positions**



**FIGURE 9****From Axial to Helical Chirality** $\angle 26^\circ$   
(AM1)

**FIGURE 10**

# **The Route to H<sub>4</sub>F<sub>4</sub> Ligands**

